UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one (SENCOR Technical): Review of a Rabbit Teratology Study Submitted by the Registrant.

Caswell No: 33D
HED Project No: 9-2295
MRID No: 412492-01

FROM: Timothy F. McMahon, Ph.D., Toxicologist 1/24/91
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

TO: PM Team 74
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head 1/28/91
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief 2/20/91
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

Registrant: Mobay Corporation

Action Requested: Review of the following Toxicology study with 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one (SENCOR Technical), required for California registration:

Rabbit Teratology Study

0001 M/T

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Conclusions:

Administration of SENCOR Technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 30 and 85 mg/kg/day, as evidenced by decreased body weight gain at the 30 mg/kg/day dose level on gestation days 18-28, and by decreased body weight gain, food consumption, and food efficiency on gestation days 7-19 at the 85 mg/kg/day dose level. Evidence was presented suggesting developmental toxicity at 10 and 30 mg/kg/day in the form of skeletal abnormalities, but was insufficient for proper interpretation.

Classification:

core supplementary

This study does not satisfy the guideline requirements (83-3) for a teratology study in rabbits.

Reviewed by: Timothy F. McMahon, Ph.D. 1/24/91
Section I, Toxicology Branch II (HFAS) (H7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 1/24/91
Section I, Toxicology Branch II (HFAS) (H7509C)

1-3625

Data Evaluation Report

Study type: Developmental Toxicity- Teratology
Species: rabbit
Guideline: 83-3

EPA ID Numbers: MRID number: 412492-01
EPA ID No: 101101-4
EPA Record No: 253329
Caswell No: 33D
HED Project No: 9-2295

Test material: 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one

Synonyms: SENCOR technical; Metribuzin

Study number(s): MTD 0100

Testing Facility: Toxicology Department, Miles Inc.
P.O. Box 40, Elkhart, IN 46515

Sponsor: Mobay Corporation, Kansas City, Missouri

Title of report: Teratology Study in the Rabbit with SENCOR Technical (Metribuzin)

Author(s): G.R. Clemens and R.E. Hartnagel Jr.

Study Completed: August 2, 1989

Conclusions: Administration of SENCOR technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 30 and 85 mg/kg/day. Evidence was presented suggesting developmental toxicity at 10 and 30 mg/kg/day in the form of skeletal abnormalities, but was insufficient for proper interpretation.

Maternal NOEL= 10 mg/kg/day
Maternal LOEL= 30 mg/kg/day (decreased body weight gain on days 18-28).

Developmental toxicity NOEL and LEL could not be determined due to a lack of information

IV. CLASSIFICATION Core supplementary

This study does not satisify the guideline requirements (83-3) for a teratogenicity study in rabbits. The following materials are requested in order to upgrade the study to core minimum:

litter incidence data for fetal skeletal abnormalities listed in Table VI of report

historical control data for the skeletal abnormalities listed in Table VI of report

necropsy findings on does not listed in Appendix D

results of histological examination of maternal tissues, if any

times and dates of sacrifice for all maternal rabbits

I. MATERIALS, METHODS, AND RESULTS

A. Test Material: 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one
purity: 92.7% a.i. (information supplied to Miles Inc. by Mobay Corporation)
description: white crystalline solid
batch #: 77-297-50

B. Vehicle: aqueous carboxymethylcellulose, composed of:

0.5% w/v carboxymethylcellulose (CMC)
0.4% w/v Tween 80
distilled water

C. Compound Stability and Homogeneity: Stability and homogeneity data on SENCOR technical dosing solutions were provided by the registrant as summary data in Appendix "B" (pages 44-48 of primary study). For homogeneity analysis, one ml aliquots of each batch were taken from the top, middle, and bottom of each batch suspension immediately after batch preparation, diluted appropriately with acetonitrile, and analyzed by HPLC. Results of homogeneity analysis are summarized in **Table 1**:

TABLE 1

Homogeneity of SENCOR Technical Dose Solutions[a]

Batch # 8831-1	Desired Concentration (mg/ml)			
	0	2.0	6.0	17.0
Found conc. (mg/ml)				
Top	0.0	2.1	6.3	17.8
Middle	-	2.0	6.1	18.4
Bottom	-	2.3	6.3	18.3

TABLE 1 (cont.)

Mean	NA	2.18± 0.16 (109)	6.30±0.10 (105)	18.2±0.28 (107)
range:	-	(100-115%)	(101-105%)	(104-108%)
Batch # 8831-2		Desired Concentration (mg/ml)		
	0	2.0	6.0	17.0
Found conc. (mg/ml)				
Top	0.0	2.1	6.3	16.8
Middle	-	1.9	6.1	17.5
Bottom	-	2.1	6.3	17.2
Mean	NA	2.06±0.07 (103)	6.28±0.11 (104)	17.1±0.34 (100)
range:	-	(99-105%)	(101-105%)	(98-102%)

[a]Data taken from report Appendix B, page 44 of registrant report. Numbers in ( ) indicate percent mean nominal concentration.

As shown in **Table 1**, the concentration of test material in batch suspensions was in the overall range of 98-115% of nominal for all concentrations tested. Concentration of test material in samples from top, middle, and bottom did not differ from one another by > 10%, with the exception of the 2.0 mg/ml batch suspension #8831-1, where one sample from the middle (2.0 mg/ml) differed from the bottom sample (2.3 mg/ml) by 13%. However, this difference is not considered significant, as the mean concentration in this batch is within 10% of nominal.

For stability analysis, test suspensions of 0.2% and 1.7% were prepared and stored covered at a mean temperature of 45 ^{o}C. On days of analysis (days 0, 10, 21, and 28 of the study), one ml aliquots were removed after allowing suspensions to reach room temperature and stirring for 20 minutes. On non-analysis days, suspensions were removed from storage for 30 minutes, stirred for 20 minutes, and then returned to storage.

At a concentration of 2.0 mg/ml (0.2%), concentration of test suspension ranged from 2.0-2.1 mg/ml over the 28 day test period. At a concentration of 17.0 mg/ml (1.7%), concentration of test suspension ranged from 17.4-18.6% over the 28 day test period. These results demonstrate the stability of test material in the dosing solution over a 28 day period (**Appendix B**, pages 47-48 of registrant report).

D. Test Animals: Species: American Dutch Rabbit, male and female (nulliparous)
Source: Langshaw Farms, Augusta, MI
Age: males, approximately 4.5 months prior to breeding; females, approximately 4.5 months prior to randomization.
Weight: males, 2.4-3.5 kg; females, 2.2-2.9 kg

E. Animal Husbandry:

A total of 16 male and 68 female rabbits were used in this study. Rabbits were housed individually in stainless steel cages in the same climate controlled room (page 10 of registrant report), and were individually identified by metal ear tag. Food (Certified Laboratory Rabbit Chow #5322, Ralston Purina Co.) and tap water were available ad libitum. Food was provided as approximately 130 g/ rabbit/day until study initiation, when exactly 130 g of food was given to each rabbit. Rabbits were acclimated at least 28 days prior to study initiation. No significant deviations were reported in environmental conditions during the study.

F. Experimental Design and Dosing:

SENCOR Technical was administered as a suspension in 0.5% CMC vehicle by gavage to female rabbits on gestation days 6 through 18 inclusive in order to assess developmental toxicity of this chemical. Prior to dose selection for the main study, a preliminary range finding study was conducted to determine a dose range for the main study.

In the preliminary range-finding study (page 102 of registrant report), doses of 0, 25, 65, 105, 145, and 185 mg/kg were administered to groups of 3 artificially inseminated does from gestation days 6 through 18. Doses of 105 mg/kg and higher resulted in significant maternal mortality and adverse reproductive effects. A slight loss in body weight gain was observed at 65 mg/kg in all treated rabbits, but no other toxicity was reported at this dose. Thus, doses below 105 mg/kg were selected for use in the main study.

Based on the results of the range finding study, doses of 0, 10, 30, and 85 mg/kg were recommended for the main teratology study. Control rabbits in the main study received 0.5% CMC vehicle. Information on assignment of rabbits to treatment groups was not provided. Dose volume was 5ml/kg. Dose volumes were based upon body weight obtained on day 6 of gestation.

Doses and numbers of rabbits tested at each dose level are as follows:

0 mg/kg/day:	17 rabbits
10 mg/kg/day:	17 rabbits
30 mg/kg/day:	17 rabbits
85 mg/kg/day:	17 rabbits

G. Mating

Four groups of 17 female rabbits (previously primed by intravenous injection of approximately 50 I.U. HCG) were artificially inseminated using semen (diluted in 0.9% saline) collected from proven bucks. A second intravenous injection of 100 I.U. HCG was given concomitantly at insemination

H. Statistical Analysis:

A copy of the statistical tests used in this study and the purposes for which they were employed is appended to this report.

I. Compliance:

A signed statement of Compliance with Good Laboratory Practice Standards was provided.

A signed "Statement of No Data Confidentiality Claims" was provided.

A signed statement of Quality Assurance was provided.

A signed statement of Flagging of Studies for Potential Adverse Effects was provided.

J. Observations:

1. Maternal Toxicity

a. Mortality

All animals were observed daily for signs of mortality.

During the dosing period, one rabbit each from the 10, 30, and 85 mg/kg dose groups died on days 27, 17, and 16, respectively. The deaths did not appear to be related to treatment with test article, but were apparently the result of either dosing trauma or systemic infection.

b. Clinical Toxicity

Animals were observed daily for signs of clinical toxicity.

A dose-related increase in the number of rabbits with stool changes (soft stool and/or reduced quantity) was observed during treatment with test article. No other clinical signs were reported in any dose group for the duration of the study. The apparent effect of test article on stool changes does not appear to be toxicologically significant.

c. Body Weight:

Body weights were recorded on day 0 of gestation (day of insemination), and on days 6, 10, 14, 18, 21, and 28 of gestation. Group mean body weights, group mean body weight gain, and individual body weight data were provided. Group mean body weight gain is shown in **Table 2**.

TABLE 2

Group Mean Body Weight Gains (kg) in SENCOR Technical-Treated Rabbits[a]

Study Interval (days)	Dose groups (mg/kg/day)			
	control	10	30	85
0-6	0.08	0.04	0.07	0.08
6-18	0.19	0.16	0.18	0.08*
18-28	0.15	0.11	0.05[b]	0.15
0-28	0.42	0.31[c]	0.33	0.31[c]

* = $p < 0.05$ vs. control by Dunnett's test. Animals which were non-pregnant were excluded from analysis.

[a]Data from Table 1, page 19 of registrant report.

[b]recalculated from Appendix C, pages 50 and 52

[c] $p < 0.05$ vs control by Student's t-test

The only treatment related effect on maternal body weight gain reported by the registrant appeared to be in rabbits in the 85 mg/kg/day dose group, where weight gain was significantly decreased relative to control during the dosing period (days 6-18). This was apparently the result of a significant difference in group mean body weight between control and high dose rabbits (3.07 vs 2.89 kg, respectively) on day 18 of the study.

According to data presented in Table 1, body weight gain over the entire gestation period did not appear to be significantly different between dose groups. However, analysis of body weight gain data between the control and the 10 and 85 mg/kg/day dose groups showed a significant ($p< 0.05$) difference in body weight gain between these groups over the entire dosing period (comparison of mean body weight gain of 0.42 kg in control vs 0.31 in the 10 and 85 mg/kg/day dose groups). The significant difference in overall weight gain between the high dose group and control is the result of the difference in weight gain between days 6-18 in these groups, while weight gain in the 10 mg/kg/day dose group was decreased vs control over the entire study period.

The post dosing weight gain for the 30 mg/kg/day dose group, while decreased from control, was not significant, due to variability of weight gain and loss within this group during this time period.

d. Food consumption

Food consumption was monitored on days 1, 6, 7, 12, 15, 19, 23, and 28. When food consumption was monitored, each rabbit received exactly 130g of food. Data on group mean food consumption

and individual food consumption were provided by the registrant. Food consumption data are summarized in the following Table (**Table 3**):

TABLE 3

Food Consumption (grams) in SENCOR Technical-Treated Rabbits[a]

Study day	Dose Group (mg/kg/day)			
	control	10	30	85
1	126.9	123.4	121.1	117.2
6	128.1	123.4	123.1	124.6
7	127.9	122.9	116.9	79.3*
12	127.3	111.9	123.8	99.3*
15	127.6	91.3	113.8	62.3*
19	127.4	120.4	124.4	111.1*
23	126.5	100.3*	109.6	114.9
28	112.8	99.8	86.4	108.1

[a]data taken from Table II, page 19 of registrant report. *$p < 0.05$ vs control (Dunnett's test).

As shown in **Table 3**, rabbits treated with 85 mg/kg/day SENCOR technical consumed significantly less food during the period of treatment, as shown by the values for food consumption on days 7 through 19. This observation concurs with the earlier mentioned observation of a decreased body weight gain during this period in the high dose group. As test article was given by oral gavage, the results of food consumption in the high dose group indicate a decreased desire to consume food following dosing. However, no clinical toxicity was reported in this dose group.

A significant decrease in food consumption was also reported for the rabbits in the 10 mg/kg/day dose group on day 23 of the study. However, this decrease appears to be the result of variability in food consumption, as well as one rabbit that was apparently sick during the latter phase of the study and died on day 27.

e. Gross Pathology

Any rabbits which died, appeared moribund or showed signs of early termination of pregnancy were submitted for complete necropsy. On day 28 of gestation, all surviving does were terminated by intravenous barbiturate overdose. The abdomen was opened, ovaries were excised, corpora lutea counted, and pregnancy determined. The uterus was removed intact and weighed. The uterus was then opened, fetuses and resorptions removed, and each implant noted. Abdominal and thoracic viscera were examined in maternal rabbits and any gross anatomical changes recorded. Tissues and/or organs showing signs of gross pathology were removed and fixed in 10% modified Millonigs buffered formalin for histologic evaluation, if necessary. Maternal organ weights were not provided.

i) Gross Observations

Necropsy findings on individual female rabbits were provided in Appendix D, page 61 of the registrant's report. There were no apparent test article related gross pathological changes in maternal rabbits at any dose level. Gross pathological changes that were observed were related primarily to those rabbits which died during the study, and included purulent peritonitis (1 rabbit from the 10 mg/kg/day dose group), dosing trauma of the lungs (1 rabbit from the 30 mg/kg/day dose group), and hemorrhagic enteritis (1 rabbit from the 85 mg/kg/day dose group). One additional rabbit from the 85 mg/kg/day dose group aborted on day 25 and was found to have pneumonia

Note: On page 14 of the registrant's report, the following statement regarding gross pathological changes in treated rabbits is made: "These changes, along with others also considered spontaneous in nature and commonly observed in this species, were observed in all groups *including control...*" (italics added). There is no evidence presented in this report that control rabbits displayed similar gross pathologic changes as treated rabbits. Infections seem to be associated only with treated rabbits.

ii) Histopathologic Observations

No histological data were provided on maternal tissues in this report.

iii) Organ Weights

No data on maternal organ weights were provided in this report.

iv) Cesarean Section Observations

Table 4: Cesarean Section Observations[a]

Dose (mg/kg/day):	0	10	30	85
#Animals Assigned	17	17	17	17
#Animals Mated/ Inseminated	17	17	17	17
Pregnancy Rate (%)	88	88	88	94
Maternal Wastage				
#Died	0	1	1	1
#Died/pregnant	0	1	1	1

Table 4 (cont.)

Dose (mg/kg/day):	0	10	30	85
#Non pregnant	2	2	2	1
#Aborted	0	0	0	1
#Premature Delivery	0	0	0	0
Whole Litter Resorptions	0	0	0	0
Total # of litters	15	14	14	14
Total Corpora Lutea	94	101	97	94
Corpora Lutea/dam	6.3	7.2	6.4	5.8
Total Implantations[b]	88	91	90	81
Implantations/Dam	5.9	6.5	6.4	5.8
Total Live Fetuses	85	84	86	77
Live Fetuses/Dam	5.7	6.0	6.1	5.5
Total Resorptions	3	7	4	4
Early	[data on early and late resorptions not provided]			
Late				
Resorptions/Dam	0.2	0.5	0.3	0.3
Total Dead Fetuses	[no dead fetuses were reported]			
Dead Fetuses/Dam				
Mean Fetal Weight (gm)	39.9	38.6	35.0[c]	39.4
% Preimplantation Loss (mean)	11.5	15.7	14.4	7.3
% Postimplantation Loss (mean)	3.6	9.9	4.1	4.6

//

Table 4 (cont.)

Sex Ratio (mean M/F)	2.8/2.8	3.0/2.9	2.9/3.2	2.5/3.0

[a]Data taken from Table III, page 20 of report and from Appendix E, page 62 of report.

[b]implantations from rabbits that died or aborted were excluded from the total.

[c]significantly different from control ($p < 0.01$) using Healy's test.

There were no apparent treatment related alterations in any of the above measured parameters suggestive of maternal toxicity. Possible developmental toxicity was evident as shown by the 11% decrease in mean fetal body weight at the 30 mg/kg/day dose level. However, this value falls within the range of historical control data on fetal body weight (page 108 of registrant report; data provided from 19 studies).

2. Developmental Toxicity

Each fetus was removed from its amniotic sac, the umbilical cord severed close to its attachment to the fetus, and viability of the fetus determined. Each fetus was then blotted bry, weighed, and subjected to a complete external examination. Following external examination, fetuses were individually identified and subjected to a comple internal examination of the abdominal and thoracic viscera, using a stereomicroscope. Skin was removed from the head for purposes of examining the eyes, and a transverse section was made through the skull posterior to the coronal suture through the cerebrum.

Following internal examination, fetuses were eviscerated and fixed in 70% ethanol. Fetuses were skinned and processed for skeletal examination using the KOH Alizarin Red-S method.

TABLE 5

Developmental Toxicity of SENCOR Technical[a]

Dose group (mg/kg/day)	0	10	30	85
Observations[a]				
#pups(litters) examined	85 (15)	84(14)	86 (14)	77(14)
#pups(litters) affected (includes external,visceral and skeletal alterations)	3 (3)	2(2)	2 (2)	3 (3)

[a] Data taken from Table VIII, page 25 of registrant report.

[a] Data taken from Table VIII, page 25 of registrant report.

a. External Malformations

Nonspecific external changes unrelated to treatment were observed in all fetuses with external abnormalities, including control fetuses. These included umbilical hernia (1 control fetus), and missing phalanges (2 fetuses from 85 mg/kg/day dose group)

b. Visceral Malformations

No treatment related visceral abnormalities were observed in any fetus from any dose group. Dilated brain ventricles were noted in 1 fetus from the 10 mg/kg/day dose group, as was a displaced vena cava in another fetus from a different litter in the same dose group.

c. Skeletal Malformations

Note: Data on the **litter incidence** of specific skeletal abnormalities were not provided.

TABLE 6

Developmental Toxicity of SENCOR Technical: Skeletal Examination[a]

Dose group (mg/kg/day)	0	10	30	85
Observations[a]				
#pups(litters) examined	85 (15)	84 (14)	86 (14)	77 (14)
skull:				
incomplete ossification	17	31[b]	38[c]	16
enlarged fontanelle	13	30[c]	36[c]	16
sternebrae				
unossified 5th sternebra	6	5	19[b]	6
scapula				
irregular spinous process	-	5	1	6[b]

Table 6 (cont.)

Dose group (mg/kg/day)	0	10	30	85
pubis incomplete ossification	8	10	27[c]	3
appendages posterior-IO Talus	3	9	23[c]	6

[a] Data are taken from Table VI, pages 23-24 of registrant report., and represent number of fetuses affected

[b] significantly different vs control by pair-wise comparison ($p < 0.05$).

[c] significantly different vs control by pair-wise comparison ($p < 0.01$)

Statistically significant increases in delayed ossification of the bones of the skull were observed in fetuses from rabbits at the 10 and 30 mg/kg/day dose level. The percent incidence rose from 20% in concurrent controls to 37 and 44% fetal incidence in the 10 and 30 mg/kg/day dose groups, respectively. This anomaly in skeletal development may be related to the increased incidence of enlarged fontanelles observed in these same dose groups, which increased from a fetal incidence of 15% in concurrent controls to 36 and 42% in the 10 and 30 mg/kg/day dose groups, respectively.

An increased incidence in incomplete ossification of the pubis as well as an unossified 5th sternebra was also observed in fetuses from SENCOR technical treated rabbits. Incomplete ossification of the pubis was significantly different from control at the 30 mg/kg/day dose level ($p< 0.01$), and the fetal incidence was 9% and 31% in concurrent controls and the 30 mg/kg/day dose group, respectively. A statistically significant increase in the incidence of unossified 5th sternebrae was also observed only in the 30 mg/kg/day dose group ($p< 0.05$). Fetal incidence of this anomaly was increased from 7% in concurrent controls to 22% in the 30 mg/kg/day dose group.

The only skeletal anomaly observed in the 85 mg/kg/day dose group which reached statistical significance was the finding of irregular spinous process at the scapular level. This anomaly was not observed to be significant at the lower dose levels.

It should be noted that on page 17 of the registrant's report, the statement is made that values for skeletal variations in the dose groups used in this study were not "outside this laboratory's historical control range and are, therefore, considered incidental." However, examination of historical control data for skeletal malformations (Appendix I, page 114 of report) shows no historical control data in support of the types of skeletal variations indicated in Table VI, pages 23-24 of the report.

II. DISCUSSION

In the present study, the developmental toxicity of SENCOR technical was assessed by oral administation of the chemical at doses of 0, 10, 30, and 85 mg/kg/day to pregnant female American Dutch Rabbits on days 6-18 of gestation inclusive. These doses were selected based upon the findings of a range-finding study conducted with SENCOR technical in this same strain of rabbit. Daily observations were made for maternal toxicity of SENCOR technical, while body weights were recorded on days 0, 6, 10, 14, 18, 21, and 28 of gestation. On day 28 of gestation, surviving rabbits were killed by intravenous barbiturate overdose and were subjected to cesarean section to assess developmental toxicity of SENCOR technical.

Minor mortality was observed in pregnant female rabbits during the study period, but was related to dosing trauma and/or infection, and not to test article administration. This is supported by the observation of no overt clinical toxicity in any rabbit at any dose level during the course of the study, with the exception of stool changes as a dose-related effect. The finding of stool changes, while dose-related, did not result in an increase in mortality with dose. This clinical effect may possibly be related to an effect on the gastrointestinal tract and/or autonomic nervous system which was not evident under the conditions of this study.

Changes in body weight gain of dosed rabbits were evident at various times during the study at all dose levels used in this study. In the 10 mg/kg/day dose group, body weight gain appeared to be depressed vs control from beginning to end of the study period. The cause of this decrement could not be determined, as there was no indication of any significant test article related toxicity in maternal or fetal rabbits at this dose. At the 30 mg/kg/day dose level, a decrease in body weight gain occurred from days 18-28, the period following dosing and prior to termination. The occurrence of this change in body weight gain during the post-dosing period would suggest some type of maternal toxicity from test article administration, although no apparent changes were observed in food consumption or clinical toxicity of maternal rabbits at this dose.

Maternal toxicity of SENCOR technical was most evident at the 85 mg/kg/day dose level. Significant reduction in maternal body weight gain occurred during the period of test article administration (days 7-19). In addition, decreased food consumption and food efficiency was also observed during this period. No other obvious signs of maternal toxicity were observed at this dose level.

Gross pathologic findings at necropsy were unremarkable in female rabbits which were examined, and did not appear test article related. However, necropsy observations were not provided for all rabbits dosed in this study (page 61 of registrant report). Furthermore, no statement regarding results of any histological examination was made. Organ weights from dosed rabbits were not provided. This dearth of information is considered a hindrance to proper evaluation of test article effects on maternal organ histology.

Most observations made at cesarean section were not significant between the control and dosed rabbits. However, a significant decrease in mean fetal body weight was observed at the 30 mg/kg/day dose level. At this dose, skeletal variations which were significantly increased in incidence from control were also observed. According to the registrant, the delay in ossification of the skeletal elements observed at this dose could be due to the decreased mean fetal body weight, i.e. delayed development. Significant increases in fetal skeletal anomalies were also observed at the 10 mg/kg/day dose level. The possibility that these increases might be due to test article administration is not supported by data from fetuses in the 85 mg/kg/day dose group, which do not follow this trend, but resemble control values. Thus, the possibility exists that the differences

observed in skeletal anomalies among fetuses from the various dose groups is due to differences in the times of sacrifice of maternal rabbits in these groups.

While evidence was provided for maternal toxicity of SENCOR technical at the 30 and 85 mg/kg/day dose levels, the fetal toxicity and teratogenicity of this compound could not be adequately evaluated in the absence of litter incidence data for fetal skeletal anomalies, times of sacrifice of the maternal rabbits in each dose group, and proper historical control data.

III.CONCLUSIONS

Administration of SENCOR technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 30 and 85 mg/kg/day. Evidence was presented suggesting developmental toxicity at 10 and 30 mg/kg/day in the form of skeletal abnormalities, but was insufficient for proper interpretation.

Maternal NOEL= 10 mg/kg/day
Maternal LOEL= 30 mg/kg/day (decreased body weight gain on days 18-28).

Developmental toxicity NOEL and LEL could not be properly ascertained due to a lack of information

IV. CLASSIFICATION Core supplementary

This study does not satisify the guideline requirements (83-3) for a teratogenicity study in rabbits. The following materials are requested in order to upgrade the study to core minimum:

litter incidence data for fetal skeletal abnormalities listed in Table VI of report

historical control data for the skeletal abnormalities listed in Table VI of report

necropsy findings on does not listed in Appendix D

results of histological examination of maternal tissues, if any

times of sacrifice for all maternal rabbits

Summary of Statistical Methods

Variable	Statistical Method Used to Compare Sencor Treated Groups to the Control Group
1. Doe Body WWeight	
- weights on Days 0, 6, 10, 14 18, 21, and 28, % weight gained (6-18 and 0-28), actual weight, and % actual weight gained	Dunnett's test
2. Food Consumption	
- food consumed on Days 1, 6, 7, 12, 15, 19, 23, and 28	Dunnett's test
3. Doe Reproductive Parameters	
- fertility index	Fisher's exact test
- gestation index	
- % viable fetuses	
- % non-viable fetuses	
- litter size	Kruskal-Wallis & Dunn's tests
- number of resorption sites	
- number viable fetuses	
- number corpora lutea	
- % male fetuses	
- number implantations	
- pre-implantation loss	
- post-implantation loss	
- average placental weight	
4. Fetal Weight Analysis	
- average combined fetal weights	Healy's test
- average male fetal weight	
- average female fetal weight	
5. Fetal Skeletal Analysis	Chi-square test, Fisher's exact test, Pair-wise
- all fetal skeletal structures with any changes were compared	
- fetal and litter incidence of malformation and select variations	Fisher's exact test